REMARKS

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claim Amendments

Claim 1 has been amended to delete "at least one compound selected from the group consisting of monoethanolamine or its pharmacologically acceptable salt".

New claim 10 has been added to the application, to recite a method for preventing occurrence of precipitation in an aqueous solution preparation. Support for new claim 10 is found on page 4, line 21 to page 5, line 1 of the specification.

Patentability Arguments

The patentability of the present invention over the disclosures of the references relied upon by the Examiner in rejecting the claims will be apparent upon consideration of the following remarks.

Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3, 4 and 6-9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Fu (U.S. Patent No. 5,414,011, hereafter "D1") in view of Ogawa (U.S. Patent No. 4,910,225, hereafter "D2"), Cagle (U.S. Patent No. 6,440,964, hereafter "D3"), and Miyagi (U.S. Patent No. 6,281,224, hereafter "D4").

This rejection is respectfully traversed.

The Position of the Examiner

The Examiner asserts that D1 teaches a stable, clear ophthalmic formulation comprising a –COOH group containing NSAID in combination with an antibiotic, a preservative, and a nonionic surfactant, wherein preferred embodiments include ketorolac, and other suitable NSAIDS include indomethacin, flurbiprofen sodium and suprofen. **The Examiner admits that D1 fails to teach bromfenac, or the inclusion of monoethanolamine or nicotinamide.**

The Examiner asserts that D2 teaches ophthalmic compositions comprising bromfenac, and states that bromfenac has a stronger anti-inflammatory effect than indomethacin.

The Examiner asserts that D3 teach cyclooxygenase type I and II inhibitors, such as diclofenac, flubiprofen, ketorolac, suprofen, bromfenac and indomethacin are preferred NSAIDs for use in ophthalmic formulations comprising an antibiotic and an NSAID.

The Examiner asserts that D4 teaches ophthalmic solutions containing the NSAID pranoprofen and an organic amine.

The Position of Applicant

Claims 1, 3, 4 and 6-9

In the presently claimed invention, (c) nicotinamide is added to prevent occurrence of precipitation in an aqueous solution preparation comprising (a) an aminoglycoside antibiotic or its pharmacologically acceptable salt and (b) bromfenac or its pharmacologically acceptable salt. By using limitation (c) in combination with limitations (a) and (b), a stable and clear aqueous solution preparation, wherein no precipitation occurs, can be obtained.

D1 discloses an opthalmologically acceptable ketorolac formulation comprising tobramycin, a quaternary ammonium preservative and a nonionic polyoxyethylated octylphenol surfactant. However, as acknowledged by the Examiner, D1 neither discloses nor suggests nicotinamide.

D2 discloses a locally administrable therapeutic composition for inflammatory disease, which is characterized by benzoylphenylacetic acid (NSAID) as an active ingredient. However, D2 also fails to disclose or suggest nicotinamide.

D3 discloses ophthalmic, otic and nasal compositions containing a new class of antibiotics such as Moxifloxacin and NSAID such as bromfenac. However, D3 also fails to disclose or suggest nicotinamide.

Therefore, none of D1-D3, nor a combination thereof, teach or suggest the combination of (a) an aminoglycoside antibiotic or its pharmacologically acceptable salt and (b) bromfenac or its pharmacologically acceptable salt **with (c) nicotinamide**, as required by Applicant's independent claim 1, and dependent claims 3, 4 and 6-9.

D4 discloses an ophthalmic solution containing **pranoprofen** (NSAID) and an organic amine, such as an alkanolamine.

As discussed above, independent claim 1 has been amended to limit component (c) to nicotinamide. D4 fails to disclose or suggest nicotinamide. Additionally, D4 fails to disclose or suggest an aminoglycoside antibiotic and bromfenac. Therefore, D4 does not remedy the deficiencies of D1-D3 as discussed above.

In D4, it is described that an alkanolamine, such as tromethamine, is preferable as an organic amine. It is also described in D4 that sulfoalkyl piperazines such as HEPES and sulfoalkyl alkylenediamines are preferably formulated in the ophthalmic solution (column 2, lines 3-13).

However, it is clear from Table 5 of the present specification (page 22), when N-methylglucamine, which is an organic amine, was added to the solution comprising bromfenac and an aminoglycoside antibiotic, **the obtained solution was slightly turbid**. Thus, even assuming *arguendo* that D4 suggests using an organic amine to obtain a stable solution of pranoprofen, this does not render obvious Applicant's presently claimed invention. Specifically, one of ordinary skill in the art would not expect that the organic amine achieves the results of the presently claimed invention, i.e., obtaining a stable and clear aqueous solution preparation, wherein no precipitation occurs.

In addition, one of ordinary skill in the art would not expect, based upon the teachings of the cited references, that nicotinamide has an effect of preventing occurrence of precipitation in the solution comprising bromfenac and an aminoglycoside antibiotic. (Please see Table 5 of the specification.)

As described above, none of D1-D4, nor a combination thereof, disclose or suggest nicotinamide, as required by Applicant's claims. Therefore, the combination of (a) an aminoglycoside antibiotic or its pharmacologically acceptable salt and (b) bromfenac or its pharmacologically acceptable salt with (c) nicotinamide is clearly not disclosed or suggested by D1-D4, or a combination thereof.

Accordingly, the subject matter of Applicant's claims 1, 3, 4 and 6-9 would not have been obvious from these cited prior art references. Withdrawal of the outstanding rejection, with respect to these claims, is kindly requested.

New Claim 10

Applicant's new claim 10 requires a method for preventing occurrence of precipitation in an aqueous solution preparation comprising an aminoglycoside antibiotic or its pharmacologically acceptable salt and bromfenac or its pharmacologically acceptable salt, which comprises adding at least one compound selected from the group consisting of monoethanolamine or its pharmacologically acceptable salt and nicotinamide to the aqueous solution preparation comprising an aminoglycoside antibiotic or its pharmacologically acceptable salt and bromfenac or its pharmacologically acceptable salt.

None of the cited references (D1-D4), nor a combination thereof, teach or suggest the method of Applicant's claim 10.

The purpose of D1 is to provide a stable and clear formulation for ketorolac and quaternary ammonium compounds benzalkonium chloride (BAC). On the other hand, the purpose of the Applicant's claimed method is to provide a stable and clear aqueous solution preparation containing an aminoglycoside antibiotic or its pharmacologically acceptable salt and bromfenac or its pharmacologically acceptable salt. (Please see page 4, lines 9 -12 of the specification.) Accordingly, the purpose of D1 is quite distinct from the purpose of Applicant's method.

Furthermore, D1fails to teach or suggest bromfenac or its pharmacologically acceptable salt, and at least one compound selected from the group consisting of monoethanolamine or its pharmacologically acceptable salt and nicotinamide, as required by new claim 10.

D1 neither discloses nor suggests "the problem to be solved" by Applicant's method, i.e., that precipitation or suspension formation occurs when an aminoglycoside antibiotic is combined with diclofenac sodium. (Please see page 2, line 29 to page 3, line 7 of the specification.) Until the present invention, with respect to a combined aqueous solution preparation comprising bromfenac and an aminoglycoside antibiotic, stable combined preparations had not yet been known, due to the difficulty in formulating the above aminoglycoside antibiotic with the non-steroidal anti-inflammatory agent. For example, when tobramycin is combined with diclofenac sodium, which is a non-steroidal anti-inflammatory agent, there is a problem that precipitation or suspension formation occurs, making it difficult to prepare an aqueous solution preparation comprising an aminoglycoside antibiotic and a nonsteroidal anti-inflammatory agent. However,

D1 does not even mention that turbidity and suspension formation occurs by adding tobramycin to the solution comprising ketorolac.

Accordingly, it follows that D1 fails to disclose or suggest that turbidity and suspension are dissolved by adding at least one compound selected from the group consisting of monoethanolamine or its pharmacologically acceptable salt and nicotinamide to the formulation, as recited in new claim 10, thereby providing a stable and clear aqueous solution without causing precipitation.

Therefore, D1 neither discloses nor suggests the method recited in new claim 10.

Although D2 describes bromfenac, the reference fails to teach or suggest that an aminoglycoside antibiotic is used to prepare the therapeutic composition. Accordingly, it follows that D2 fails to disclose or suggest that turbidity and suspension formation occurs in a combined aqueous solution preparation comprising bromfenac and an aminoglycoside antibiotic. Thus, D2 fails to disclose or suggest the purpose of Applicant's claimed method.

Similar to the discussion of D1 above, D2 also fails to disclose or suggest "the problem to be solved" by Applicant's method.

Further, D2 fail to teach or suggest "at least one compound selected from the group consisting of monoethanolamine or its pharmacologically acceptable salt and nicotinamide", as required by Applicant's new claim 10. Thus, D2 fails to describe that a stable and clear aqueous solution, without causing precipitation, can be provided by adding monoethanolamine or its pharmacologically acceptable salt, or nicotinamide to an aqueous solution preparation comprising bromfenac and an aminoglycoside antibiotic.

Therefore, D2 also fails to disclose or suggest the method recited in new claim 10.

Similar to the discussion regarding D1 and D2, D3 also fails to disclose or suggest providing a clear and stable aqueous solution preparation. Additionally, there is no mention or suggestion in D3 about the purpose and effect of the presently claimed invention, or "the problem to be solved" by the presently claimed invention.

Accordingly, the method of new claim 10 is also unobvious over D3.

D4 neither discloses nor suggests "an aminoglycoside antibiotic or its pharmacologically acceptable salt" nor "bromfenac or its pharmacologically acceptable salt". Thus, it follows that D4 fails to disclose or suggest that turbidity and suspension formation occurs in a combined

aqueous solution preparation comprising bromfenac and an aminoglycoside antibiotic. Therefore, D4 also fails to disclose or suggest the purpose of the presently claimed invention, and "the problem to be solved" by the presently claimed invention.

Accordingly, the method of new claim 10 is also unobvious over D4.

As described above, D1-D4 neither disclose nor suggest the method for preventing occurrence of precipitation in an aqueous solution preparation, which comprises adding at least one compound selected from the group consisting of monoethanolamine or its pharmacologically acceptable salt and nicotinamide to the aqueous solution comprising an aminoglycoside antibiotic or its pharmacologically acceptable salt and bromfenac or its pharmacologically acceptable salt.

Therefore, even if the teachings of D1-D4 are combined, the invention recited in new claim 10 would not have been obvious to one of ordinary skill in the art.

Conclusion

Therefore, in view of the foregoing amendments and remarks, it is submitted that the ground of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

If, after reviewing this Amendment, the Examiner feels there are any issues remaining which must be resolved before the application can be passed to issue, the Examiner is respectfully requested to contact the undersigned by telephone in order to resolve such issues.

Respectfully submitted,

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